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Therapeutic antibody engineering

Current and future advances driving the strongest growth area in the pharmaceutical industry

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It is an important event in any knowledge area when an authority in the field decides that it is time to share all accumulated knowledge and learnings by writing a text book. This does not occur often in the biopharmaceutical industry, likely due to both the highly dynamic environment with tight timelines and policies and procedures at many pharmaceutical companies that hamper knowledge sharing. To take on a task like this successfully, a strong drive combined with a desire and talent to teach, but also an accommodating and stimulating environment is required. Luckily for those interested in therapeutic monoclonal antibodies, Dr. William R. Strohl decided about two years ago that the time was right to write a book about the past, present and future of these fascinating molecules. Dr. Strohl's great expertise and passion for biotechnology is evident from his life story and his strong academic and industry track record. Dr. Strohl pioneered natural product biotechnology, first in academia as a full professor of microbiology and biochemistry at Ohio State University in Columbus, Ohio and later in industry while at Merck. Despite his notable advances in recombinant natural products, industry interest in this area waned and in 2001 Dr. Strohl sought new opportunities by entering the field of antibody therapeutics. He initiated antibody discovery through phage display at Merck, and then moved to Centocor Research and Development Inc. (now Janssen Biotech, Inc.) in 2008 to head Biologics Research, where he now directs the discovery of innovative therapeutic antibody candidates.

Completion of a book with the breadth and depth of *Therapeutic Antibody Engineering: Current and Future Advances Driving the Strongest Growth Area in the Pharmaceutical Industry* is a remarkable achievement for a single author. It speaks for Dr. Strohl's passion for science, and power of persuasion, that he found the time required by convincing his family that writing a text book about antibodies would be good way to spend quality time together. Dr. Strohl teamed up with his wife Lila Strohl, who is a gifted professional medical illustrator with over 20 years of experience, and his son Joshua, who assisted with the impressive reference section of the book. From the text and art work, it is clear that Dr. Strohl made a considerable effort to explain the essentials of therapeutic antibody biology to his familial collaborators, and thereby to us, the readers of his book. *Therapeutic Antibody Engineering* thereby represents a unique project, resulting in a book that reads very well despite its highly compact writing and copious references. Lila Strohl's drawings strongly support the text and stand out as they highlight, in correct dimensions, critical features of antibody, target and effector molecule structures and complexes as we understand them today. Of special interest are the many summary tables, which provide clear and complete overviews of key information.

An important feature of the book is that the chapters are written as stand-alone reviews, with the first nine chapters

providing necessary background on antibody structure, mechanisms of action, effector functions and relevant discovery technologies. The chapters in the second half of the book provide a detailed guide to antibody engineering for therapeutic use; these do not need to be read sequentially and can be studied on an as-needed basis. As a true innovator, Dr. Strohl puts emphasis on all the "firsts" in therapeutic antibody development, providing a strong historic perspective next to highlights of the critical importance of rapid innovation in our field.

The first three chapters provide an introduction to antibody biology and structure-function relationships, the therapeutic antibody naming convention (critical for those not familiar with the jawbreakers common in the field), as well as the therapeutic antibody development process and its commercial aspects. This section brings home not only the large number of patients in diverse therapeutic areas who benefit from antibody drugs, but also the accompanying commercial success of antibody therapeutics. It defines the historical and future growth areas of antibody therapeutics in comparison to that of small molecule drugs. Dr. Strohl's analyses of the success and potential of therapeutic antibodies, founded by cogent arguments, will likely inspire students interested in drug development to enter the field. For people working on small molecules, it may be a wake-up call to think of a career change, whereas for those of us already involved in the science and business of therapeutic antibodies, it provides a feel-good outlook, but also describes the many challenges and opportunities ahead.

Chapters 4 through 6 describe the fundamentals of antibody technology and antibody diversity, including how antibody variable region diversity from various species can be harvested, selected and engineered to generate therapeutic antibody drug candidates and products. Interestingly, Dr. Strohl points out the role that patents (or sometimes lack thereof) have played in antibody development. Initially, the decision not to patent Köhler and Milstein's seminal discovery of hybridoma technology, as their intellectual property office surprisingly viewed it as a technology lacking commercial application, allowed rapid adaptation and progress. Patents on the other hand, when combined with sound commercial strategies, have allowed the generation of many innovative products made possible by novel technologies such as phage display, humanization and human antibody transgenic mice. Dr. Strohl also makes the interesting point that the time required for new key technologies to be incorporated into FDA-approved therapeutic proteins is about the same as the average development time for a biologic. The application of new technologies in marketed biologics is therefore incredibly fast. This provides a strong driver for the success of innovator companies who develop or rapidly adopt novel enabling technologies for the development of novel and meaningful therapeutics.

Chapters 7 and 8 give an excellent overview of the importance of interactions with effector molecules for antibody mechanism of action and in vivo half-life. Therapeutic antibodies are classified into groups by virtue of at least seven mechanisms of action. The information summarized in the tables, figures and drawings provide a superb reference. Chapter 8 also provides analysis of the various targets recognized by therapeutic antibodies in development and on the market, amounting to a total of about 69 unique soluble and 105 unique membrane targets being addressed. A rough analysis suggests the number of potential druggable targets to be a multiple of this. Dr. Strohl therefore expresses the view that many targets for therapeutic antibodies or antibody-like molecules are still available. A major obstacle, however, is a lack of proven biology and involvement in disease pathology.

Chapters 9 through 11 review the various antibody classes and the optimization of Fc function to improve their performance. The majority of the 75 antibodies and Fc-fusion proteins on the market or in advanced clinical trials are based on natural IgG1 molecules. Other isotypes are underutilized and, interestingly, are surpassed in number by molecules with an engineered Fc. This indicates the high importance of antibodies with optimized Fc function or pharmacology for the generation of novel, more potent therapies. Antibody format improvements through protein or glycoengineering are reviewed in detail and their applicability discussed. Future antibody innovation challenges include the potential to harness the advantages of IgM and IgA antibodies in terms of valency, potency and mucosal surface delivery, as well as further antibody format optimization to allow the targeting of specific tissues. Although these approaches still lack clinical validation, they provide strong opportunities for the generation of more effective future antibody therapeutics.

Chapter 12 reviews therapeutic antibody fragments. While the first antibody fragment approved for human use was a Fab fragment with a novel mechanism of action, the development of therapeutic molecules in this class has thereafter been limited to differentiated follow-ons, such as fragments targeting tumor necrosis factor or vascular endothelial growth factor. Dr. Strohl clearly summarizes the strategic reasons that form the basis of a decision to develop an antibody fragment rather than a whole antibody. These include target-product profiles, which require a short half-life, absence of effector function, monovalency or the potential as an engineering scaffold. Approaches to extend half-life of molecules in this class are also discussed.

Chapter 13 discusses both polyclonal antibody approaches and engineered multispecific molecules. This seems like a non-obvious choice because the former approach encompassing serum therapies and intravenous immunoglobulin is traditional and conservative. In fact, the new defined polyclonal mixtures can be considered extensions taught by the classical intravenous immunoglobulin concept. Engineered multispecific antibodies, by comparison, are novel entities that emerged from appreciating the polypharmacology of many human diseases. In this respect, the classification of multispecific antibodies by their intended mechanism of action, instead of their molecular structures, might have been more straightforward. Indeed, bispecific recruiter antibodies, such as BITEs, TandAbs, and MM-111 share many challenges with early antibody-drug conjugates, whereas dual-ligand or receptor blockers should be compared

with antibody mixtures. Given this heterogeneity, the statement of potentially lower therapeutic indexes for multispecific antibodies (e.g., due to partially overlapping minimally effective and maximally tolerated concentrations of the respective separate entities) seems too general. A better understanding of the pharmacology of multispecific antibodies clearly represents a critical area of future study.

Antibody-drug conjugates arguably represent one of the fastest therapeutic antibody growth areas. Chapter 15 discusses target, antibody scaffold, linker and toxin selection, which are all critical for optimal antibody-drug conjugate activity, as well as lessons learned and focus areas for future exploration.

Developability, manufacturing and animal testing are discussed in chapters 16–18. Developability is an essential attribute of a successful biologic and the term defines an aggregate concept that includes stability, solubility and consistency of biophysical, biochemical and bioactivity profiles between different batches. Because antibodies exist as complex mixtures of heterogeneous isoforms, these variables cannot be assumed to be easily controlled. Dr. Strohl discusses the factors that can render antibodies undevelopable and provides best practices in producing "manufacturable" antibodies. Current manufacturing platforms and emerging trends are discussed. In addition, he reviews the concepts of immunogenicity and biocomparability, which are particularly important for the emerging field of biosimilar antibody therapeutics. Indeed, a significant portion of efficacy and safety of antibody therapeutics are determined by their pharmacology. Interestingly, the interaction of antibodies with effector molecules in rodents is relatively well understood, whereas interactions with the immune system of rhesus macaque and cynomolgus monkey are less well understood. This is an important knowledge gap in the field that needs to be closed.

The final chapter is dedicated to challenges and opportunities for antibody drugs of the future. Here, Dr. Strohl draws on his extensive experience in antibody discovery and development to discuss current trends in the field, including commoditization of discovery technologies, paucity of novel antibody targets, penetration of small molecules into therapeutic areas currently dominated by antibodies, reimbursement pressures, emergence of "tuned for purpose" antibody-like molecules, need for companion diagnostics, expansion of marketing efforts to emerging markets, and associated biosimilar and follow-on-biologic challenges. The author warns against complacency triggered by the robust growth of antibodies therapies in the past 15 years and suggests that concerted "biology-first" efforts are needed to fully harvest the promise and excitement of "fit-for-purpose" antibody-like molecule drugs in the coming decade.

As should be clear from this review, we thoroughly enjoyed reading *Therapeutic Antibody Engineering: Current and Future Advances driving the strongest Growth Area in the Pharmaceutical Industry*. Dr. Strohl found an excellent balance between readability and depth of the material covered and we expect that his book will be popular with students as well as practitioners in the field of antibody drug development and human health. The book is well-referenced and provides plentiful opportunities to continue subject-specific learning. Lila Strohl's realistic drawings and the extensive tables that summarize state-of-the art knowledge and highlight critical features are an excellent supplement to the text. Overall, we found little to suggest as improvements to the book, although, with the rapid developments in our field, an updated version will be needed soon. This is certainly something to look forward to, especially as we hope that it could come as a full-color edition.